

Cataracts

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## ABSTRACTS

Inhibitory effect of melatonin on cataract formation in newborn rats: evidence for an antioxidative role for melatonin.

Abe M, Reiter RJ, Orhii PB, et al.

*J Pineal Res.* 1994 Sep; 17(2):94-100.

We evaluated the inhibitory effect of melatonin, a recently discovered scavenger of free radicals, on cataract formation in the newborn rat. The glutathione synthesis inhibitor, buthionine sulfoximine (BSO) (3 mmol/kg), was intraperitoneally injected into newborn rats for 3 consecutive days starting on day 2 after birth. These glutathione depleted rats develop cataracts. Melatonin (4 mg/kg) was injected intraperitoneally into half of the rats once a day beginning at day 2 after birth; the other half of the animals received solvent daily. The incidence of cataract was observed on day 16, after the eyes of the newborn animals had opened. Both reduced glutathione (GSH) and oxidized glutathione (GSSG) levels were measured. Cataracts were observed in all animals (18/18) treated with BSO plus solvent. The incidence of the cataract in the animals cotreated with melatonin was only 6.2% (1/15). Total lenticular glutathione (GSH + GSSG) levels in BSO only treated rats were reduced by 97%. The total glutathione in the lens of the BSO plus melatonin group was significantly higher (by 3%) than that of the BSO only group. The percentage of the total glutathione as GSSG for the BSO plus solvent group was higher than the control value. Cotreatment of BSO injected rats with melatonin (4 mg/kg/day) clearly reduced cataract formation proving that it is directly or indirectly protective against oxidative stress which accompanies glutathione deficiency. The inhibitory effects of melatonin on cataract formation in this study could be due to melatonin's free radical scavenging activity or due to its stimulatory effect on glutathione production

[Treatment of the disorders of aging with Ginkgo biloba extract. From pharmacology to clinical medicine].

Allard M.

*Presse Med.* 1986 Sep 25; 15(31):1540-5.

Ginkgo biloba extract is prescribed in psychic and behavioural disorders of the elderly, in peripheral vascular deficiency and in functional disorders of ischaemic origin in the E.N.T. and eye areas. Numerous controlled clinical trials justify these prescriptions and are in agreement with the pharmacological data currently available. Experimentally, Ginkgo biloba extract has proved active on the circulatory and rheological functions, on neuronal metabolism threatened by ischaemia or hypoxia, on neurotransmission and on membrane lesions caused by free oxygenated radicals. Concerning Alzheimer's disease and dementia, no firm conclusion can be drawn for the time being due to the lack of animal model. However, experimental data suggest that the product may act on a number of major elements of these diseases. From what is already known about Ginkgo biloba extract, it appears that it fulfills the conditions laid down by the W.H.O. concerning the development of drugs effective against cerebral ageing

Antioxidants and cataract: (cataract induction in space environment and application to terrestrial aging cataract).

Bantsev V, Bhardwaj R, Rathbun W, et al.

*Biochem Mol Biol Int.* 1997 Sep; 42(6):1189-97.

The effect of several antioxidants and cysteine-elevating precursor drugs (prodrugs) was tested on lens damage occurring after in vitro exposure to low levels of <sup>60</sup>Co-gamma-irradiation, to simulate in vitro the exposure to radiation in vivo of (1) astronauts (2) jet crews (3) military radiation accident personnel. Tocopherol (100 microM), ascorbic acid (1 mM), R-alpha-lipoic acid (1 mM), and taurine (0.5 mM) protected against radiation-associated protein leakage. MTCA and ribocysteine protected lenses against opacification, LDH and protein leakage, indicating that antioxidants and prodrugs of cysteine appear to offer protection against lens damage caused by low level radiation

A prospective study of carotenoid intake and risk of cataract extraction in US men.

*Am J Clin Nutr.* 1999 Oct; 70(4):517-24.

**BACKGROUND:** Dietary antioxidants, including carotenoids, are hypothesized to decrease the risk of age-related cataracts by preventing oxidation of proteins or lipids within the lens. However, prospective epidemiologic data concerning this phenomenon are limited. **OBJECTIVE:** Our objective was to examine prospectively the association between carotenoid and vitamin A intakes and cataract extraction in men. **DESIGN:** US male health professionals (n = 36644) who were 45-75 y of age in 1986 were included in this prospective cohort study. Others were subsequently included as they became 45 y of age. A detailed dietary questionnaire was used to assess intake of carotenoids and other nutrients. During 8 y of follow-up, 840 cases of senile cataract extraction were documented. **RESULTS:** We observed a modestly lower risk of cataract extraction in men with higher intakes of lutein and zeaxanthin but not of other carotenoids (alpha-carotene, beta-carotene, lycopene, and beta-cryptoxanthin) or vitamin A after other potential risk factors, including age and smoking, were controlled for. Men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract relative to men in the lowest fifth (relative risk: 0.81; 95% CI: 0.65, 1.01; P for trend = 0.03). Among specific foods high in carotenoids, broccoli and spinach were most consistently associated with a lower risk of cataract. **CONCLUSIONS:** Lutein and zeaxanthin may decrease the risk of cataracts severe enough to require extraction, although this relation appears modest in magnitude. The present findings add support for recommendations to consume vegetables and fruit high in carotenoids daily

Carnosine reacts with a glycated protein.

Brownson C, Hipkiss AR.

*Free Radic Biol Med.* 2000 May 15; 28(10):1564-70.

Oxidation and glycation induce formation of carbonyl (CO) groups in proteins, a characteristic of cellular aging. The dipeptide carnosine (beta-alanyl-L-histidine) is often found in long-lived mammalian tissues at relatively high concentrations (up to 20 mM). Previous studies show that carnosine reacts with low-molecular-weight aldehydes and ketones. We examine here the ability of carnosine to react with ovalbumin CO groups generated by treatment of the protein with methylglyoxal (MG). Incubation of MG-treated protein with carnosine accelerated a slow decline in CO groups as measured by dinitrophenylhydrazine reactivity. Incubation of [(14)C]-carnosine with MG-treated ovalbumin resulted in a radiolabeled precipitate on addition of trichloroacetic acid (TCA); this was not observed with control, untreated protein. The presence of lysine or N-(alpha)-acetylglycyl-lysine methyl ester caused a decrease in the TCA-precipitable radiolabel. Carnosine also inhibited cross-linking of the MG-treated ovalbumin to lysine and normal, untreated alpha-crystallin. We conclude that carnosine can react with protein CO groups (termed "carnosinylation") and thereby modulate their deleterious interaction with other polypeptides. It is proposed that, should similar reactions occur intracellularly, then carnosine's known "anti-aging" actions might, at least partially, be explained by the dipeptide facilitating the inactivation/removal of deleterious proteins bearing carbonyl groups

[A glutathione deficiency in open-angle glaucoma and the approaches to its correction].

Bunin AI, Filina AA, Elichev VP.

*Vestn Oftalmol.* 1992 Jul; 108(4-6):13-5.

A total of 151 patients with open-angle glaucoma, 23 ones with closed angle glaucoma, and 57 ones with age-associated cataracts were examined. The reference group consisted of 21 subjects with posttraumatic cataracts (1.5 years after the injury) and normal subjects. Nonprotein sulfhydryl groups (glutathione) were measured in the peripheral blood, aqueous humor, and in tissue samples from the scleral drainage sites, obtained in antiglaucoma surgery and in surgery for cataract extraction. Aqueous humor of patients with posttraumatic cataracts, blood samples of these patients and normal subjects were examined for control. The level of sulfhydryl groups was found significantly lowered in the anterior chamber humor of patients with open-angle glaucoma, particularly in those with disease Stages II and III as against the controls. The content of sulfhydryl groups was lowered in the tissue samples from the scleral drainage area of patients with open-angle glaucoma Stages II and III vs. that in the patients with Stage I condition. Similar changes were found in the red cells of patients with Stages II and III open-angle glaucoma. Glutathione is an important component of the cellular antioxidant system. The findings point to a reduction of the processes of antioxidant defense of ocular tissues, developing as early as in the first stage of open-angle glaucoma. Lipoic acid administration for 2 months was associated with a rise of glutathione level in the red cells of patients with Stages II and III open-angle glaucoma

Taurine: its biological role and clinical implications.

Chesney RW.

*Adv Pediatr.* 1985; 32:1-42.

More than simply cataloging the numerous experimental models in which taurine plays a modulating role, this discussion aims at stimulating further investigation of the potential clinical value of this abundant sulfur amino acid. Both the biomedical investigator and clinician must be struck by the enormous amount of taurine floating freely in the intracellular water of the cells. In cardiac tissue alone, taurine levels of 20 mM or higher may be found. Given this abundance of taurine, why is our understanding of its function so elusive? Although it is clear taurine is important in conjugating bile acids to form water-soluble bile salts, only a fraction of available taurine is used for this function, predominantly in young animals and children. While taurine conjugation is the preferred route of bile acid conjugation in the young, changes in adults given 250 mg of taurine daily for two to three weeks are insignificant. Total pool size of bile acid and chenodeoxycholic acid declines. Unchanged are the rate of bile acid synthesis or the secretion rates of biliary cholesterol, bile acid and phospholipids. Biliary cholesterol saturation also stays the same. The finding that taurine availability protects against cholestasis induced by monohydroxy bile acids remains confined to guinea pigs. The abundance of taurine suggests it may be an osmoregulator of cell volume, and there is convincing evidence that it serves this function in fish. Taurine may play this role in the brain under high osmotic states such as hypernatremia, dehydration and uremia. Evidence is strong that taurine is vital in maintaining retinal function, which may explain why taurine is so abundant in human breast milk. Prolonged TPN feeding of infants demonstrates the importance of taurine in retinal development. We have begun to appreciate the role of the kidney in conserving taurine and how this is perturbed in the neonatal period. Taurine has recently been added to infant formulas (about 50 mg/L). Cataloging what we know of taurine function, however, produces a list of "maybes." Now is the time for exhaustive, careful taurine research that will produce more definite answers

Taurine: is it required for infant nutrition?

Chesney RW.

*J Nutr.* 1988 Jan; 118(1):6-10.

Antioxidant vitamins and age-related eye disease.

Christen WG.

*Proc Assoc Am Physicians.* 1999 Jan; 111(1):16-21.

Basic research studies suggest that oxidative mechanisms may play an important role in the pathogenesis of cataract and age-related macular degeneration, the two most important causes of visual impairment in older adults. These findings raise the possibility that vitamins and trace minerals with antioxidant properties can be of benefit in preventing the onset or progression of disabling eye disease. Results from observational epidemiological studies in humans, however, are inconclusive. Although findings from several studies, primarily cross-sectional and case-control, are generally compatible with a possible protective role for micronutrients in disease development, the data for specific nutrients or specific disease types are inconsistent. The imprecision of dietary exposure data and the likely effects of uncontrolled confounding further limit these observational studies. Well-designed, large-scale, randomized trials are required to evaluate definitively the potentially important benefit of vitamin supplementation in eye disease

Macular pigment optical density in a midwestern sample.

Ciulla TA, Curran-Celantano J, Cooper DA, et al.

*Ophthalmology.* 2001 Apr; 108(4):730-7.

**OBJECTIVE:** To assess the distribution of the macular pigments (MPs) lutein (L) and zeaxanthin (Z) in a healthy sample more representative of the general population than past studies and to determine which dietary factors and personal characteristics might explain the large interindividual differences in the density of these MPs. **DESIGN:** Prevalence study in a self-selected population. **PARTICIPANTS:** Two hundred eighty healthy adult volunteers, consisting of 138 men and 142 women, between the ages of 18 and 50 years, recruited from the general population. **METHODS:** MP optical density was measured psychophysically at 460 nm by use of a 1 degree test field. Serum was analyzed for carotenoid and vitamin E content with reversed-phase high-performance liquid chromatography. Usual intakes of nutrients over the past year were determined by means of a food frequency questionnaire. **MAIN OUTCOME MEASURES:** MP optical density. **RESULTS:** Mean MP optical density measured 0.211 +/- 0.13, which is approximately 40% lower than the average reported in smaller, less representative studies. MP density was 44% lower in the bottom versus the top quintile of serum L and Z concentrations. Similarly, MP density was 33% lower in the bottom compared with the top quintile of L and Z intake. MP density was 19% lower in blue-grey-eyed subjects than in subjects with brown-black irises. When all variables were considered together in a general linear model of determinants of MP, statistically

significant ( $P < 0.05$ ) relationships were found between MP density and serum L and Z, dietary L and Z intake, fiber intake, and iris color. CONCLUSIONS: These data suggest that MP values in this healthy adult population are lower than in smaller select samples. Moreover, these data indicate that MP is related to serum L and Z, dietary L and Z intake, fiber intake, and iris color

Nutritional factors in degenerative eye disorders: cataract and macular degeneration.

Gaby AR.

*J Adv Med.* 1993;27-39.

H<sub>2</sub>O<sub>2</sub>-induced uncoupling of bovine lens Na<sup>+</sup>,K<sup>+</sup>-ATPase.

Garner WH, Garner MH, Spector A.

*Proc Natl Acad Sci U S A.* 1983 Apr; 80(7):2044-8.

A 1-hr exposure of bovine lenses in organ culture to H<sub>2</sub>O<sub>2</sub> concentrations in the range found in the aqueous fluid of patients with cataracts inhibits 86Rb<sup>+</sup> influx. At 1 mM H<sub>2</sub>O<sub>2</sub>, complete inhibition was observed and further investigated. Membrane permeability is slightly decreased. Although lactate concentrations increase 2-fold, lens ATP concentrations decrease approximately equal to 10%, suggesting that glycolysis may be stimulated but ATP production is not able to keep up with the demand for energy. Examination of epithelial cell Mg<sup>2+</sup>-stimulated Na<sup>+</sup>,K<sup>+</sup>-ATPase isolated from the cultured lenses indicates H<sub>2</sub>O<sub>2</sub>-induced modification. At 5 mM MgATP, ATP hydrolysis is accelerated 30%; at 3 mM MgATP, hydrolysis is normal; and at 0.75 mM MgATP, it is inhibited 75%. p-Nitrophenyl phosphate hydrolysis and eosin maleimide binding indicate that K<sup>+</sup> control of the enzyme is modified. Thus, a very early effect of H<sub>2</sub>O<sub>2</sub> upon the lens, well before the formation of opacity, appears to be the uncoupling of Na<sup>+</sup> and K<sup>+</sup> transport from ATP hydrolysis

Nutritional requirement for taurine in patients receiving long-term parenteral nutrition.

Geggel HS, Ament ME, Heckenlively JR, et al.

*N Engl J Med.* 1985 Jan 17; 312(3):142-6.

Animals fed diets lacking the amino acid taurine have low plasma and tissue levels of taurine and ultimately have retinal dysfunction. Since parenteral nutrition does not ordinarily provide taurine, we looked for evidence of taurine deficiency in 21 children and 23 adults undergoing long-term parenteral nutrition at home for an average of 27 +/- 23 (S.D.) months. The fasting plasma taurine level was reduced in children as compared with controls (26 +/- 13 vs. 57 +/- 16 μmol per liter, P less than 0.001). In adults with less than 25 per cent intestinal absorption of the recommended caloric intake, the plasma taurine level was also significantly reduced and correlated inversely with the duration of parenteral nutrition. Electroretinograms were abnormal in each of eight children who were examined. Addition of taurine to the intravenous solutions restored plasma levels to normal in four children; the electroretinograms of three of these children also became normal. The plasma taurine level became abnormally low again in two of three children one year after the intravenous taurine was discontinued. We conclude that children and possibly adults receiving long-term parenteral nutrition have a nutritional requirement for taurine

Antioxidant vitamins in cataract prevention.

Gerster H.

*Z Ernährungswiss.* 1989 Mar; 28(1):56-75.

The ocular lens, which is continually exposed to light and ambient oxygen, is at high risk of photooxidative damage resulting in cataract. Oxygen free radicals appear to impair not only lens crystallins which will aggregate and precipitate forming opacities but also proteolytic enzymes whose function it would be to eliminate the damaged proteins. Apart from an enzymatic defense system consisting of superoxide dismutase, catalase and glutathione peroxidase against excited oxygen species the lens contains the antioxidant vitamins C, E and presumably beta-carotene as another line of defense. In vitro and in vivo studies in different animal species have demonstrated a significant protective effect of vitamins C and E against light-induced cataract. Sugar and steroid cataracts were prevented as well. Epidemiological evidence in humans suggests that persons with comparatively higher intakes or blood concentrations of antioxidant vitamins are at a reduced risk of cataract development. These positive findings established by several research groups justify extensive intervention trials with antioxidant vitamins in humans using presenile cataract development as a model

Retinal degeneration associated with taurine deficiency in the cat.

Hayes KC, Carey RE, Schmidt SY.

*Science*. 1975 May 30; 188(4191):949-51.

A degeneration of the retinal photoreceptor cells develops in cats when casein is the source of dietary protein. Amino acid profiles indicate that the degeneration is associated with a selective decrease in plasma and retinal taurine concentrations. A sulfur amino acid deficit in the casein diet combined with specific amino acid requirements of the cat appear related to this unique expression of taurine deficiency

Natural therapies for ocular disorders, part two: cataracts and glaucoma.

Head KA.

*Altern Med Rev*. 2001 Apr; 6(2):141-66.

Pathophysiological mechanisms of cataract formation include deficient glutathione levels contributing to a faulty antioxidant defense system within the lens of the eye. Nutrients to increase glutathione levels and activity include lipoic acid, vitamins E and C, and selenium. Cataract patients also tend to be deficient in vitamin A and the carotenes, lutein and zeaxanthin. The B vitamin riboflavin appears to play an essential role as a precursor to flavin adenine dinucleotide (FAD), a co-factor for glutathione reductase activity. Other nutrients and botanicals, which may benefit cataract patients or help prevent cataracts, include pantethine, folic acid, melatonin, and bilberry. Diabetic cataracts are caused by an elevation of polyols within the lens of the eye catalyzed by the enzyme aldose reductase. Flavonoids, particularly quercetin and its derivatives, are potent inhibitors of aldose reductase. Glaucoma is characterized by increased intraocular pressure (IOP) in some but not all cases. Some patients with glaucoma have normal IOP but poor circulation, resulting in damage to the optic nerve. Faulty glycosaminoglycan (GAG) synthesis or breakdown in the trabecular meshwork associated with aqueous outflow has also been implicated. Similar to patients with cataracts, those with glaucoma typically have compromised antioxidant defense systems as well. Nutrients that can impact GAGs such as vitamin C and glucosamine sulfate may hold promise for glaucoma treatment. Vitamin C in high doses has been found to lower IOP via its osmotic effect. Other nutrients holding some potential benefit for glaucoma include lipoic acid, vitamin B12, magnesium, and melatonin. Botanicals may offer some therapeutic potential. Ginkgo biloba increases circulation to the optic nerve; forskolin (an extract from *Coleus forskohlii*) has been used successfully as a topical agent to lower IOP; and intramuscular injections of *Salvia miltiorrhiza* have shown benefit in improving visual acuity and peripheral vision in people with glaucoma

Carnosine reacts with protein carbonyl groups: another possible role for the anti-ageing peptide?

Hipkiss AR, Brownson C.

*Biogerontology*. 2000; 1(3):217-23.

Carnosine (beta-alanyl-L-histidine) can delay senescence and provoke cellular rejuvenation in cultured human fibroblasts. The mechanisms by which such a simple molecule induces these effects is not known despite carnosine's well documented antioxidant and oxygen free-radical scavenging activities. Carbonyl groups are generated on proteins post-synthetically by the action of reactive oxygen species and glycating agents and their accumulation is a major biochemical manifestation of ageing. We suggest that, in addition to the prophylactic actions of carnosine, it may also directly participate in the inactivation/disposal of aged proteins possibly by direct reaction with the carbonyl groups on proteins. The possible fates of these 'carnosinylated' proteins including the formation of inert lipofuscin, proteolysis via the proteasome system and exocytosis following interaction with receptors are also discussed. The proposal may point to a hitherto unrecognised mechanism by which cells/organisms normally defend themselves against protein carbonyls

Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention.

Jacques PF, Chylack LT, Jr.

*Am J Clin Nutr*. 1991 Jan; 53(1 Suppl):352S-5S.

The relationship between antioxidant nutrient status and senile cataract was examined in 77 subjects with cataracts and 35 control subjects with clear lenses. Subjects with low (below the 20th percentile) and moderate (20th-80th percentiles) plasma nutrient and nutrient intake levels of vitamin C, vitamin E, and carotenoids were compared with subjects with high levels (above the 80th percentile). The odds ratio (OR) of cortical (CX) cataract among subjects with low plasma carotenoid levels was 7.2 (P less than 0.05) and the OR of posterior subcapsular (PSC) cataract for persons with low plasma vitamin C was 11.3 (P less than

0.10). Low vitamin C intake was associated with an increased risk of CX (OR = 3.7, P less than 0.10) and PSC (OR = 11.0, P less than 0.05) cataract. Subjects who consumed fewer than 3.5 servings of fruit or vegetables per day had an increased risk of both CX (OR = 5.0, P less than 0.05) and PSC cataract (OR = 12.9, P less than 0.01)

[Antioxidants for prophylaxis of eye diseases].

Kaluzny J.

*Klin Oczna.* 1996 Feb; 98(2):141-3.

The contemporary literature has widely described the role of free oxygen radicals and their antioxidants in pathogenesis of some eye diseases, mainly cataract, age-related macular degeneration, retinopathy of prematurity and cystic macular oedema. This paper presents publications which stress the importance of antioxidants use in prophylaxis of cataract and age-related macular degeneration. Positive antioxidants role was proved both in experimental research and in clinical observations

[Contemporary views on the pathogenesis and possible prophylaxis of age related cataracts].

Kaluzny JJ, Kaluzny J.

*Pol Merkuriusz Lek.* 1997 Jan; 2(7):76-8.

In this review the role of UVB/290-320 nm/ and visible light radiation in generating of free radicals in the lens is described, which is the main factor leading to development of senile cataract. Also the mechanisms of antioxidant defence are presented especially glutathione and ascorbic acid. We review the literature connected with diet supplementation of antioxidants /vit. E, C, selenium/. According to actual theories the use of sun-glasses with UVB-filters, and antioxidant diet supplementation seems to be useful in prevention of age-related cataract

Inhibition of nitric-oxide synthase 2 by aminoguanidine provides neuroprotection of retinal ganglion cells in a rat model of chronic glaucoma.

Neufeld AH, Sawada A, Becker B.

*Proc Natl Acad Sci U S A.* 1999 Aug 17; 96(17):9944-8.

Glaucoma is an optic neuropathy with cupping of the optic disk, degeneration of retinal ganglion cells, and characteristic visual field loss. Because elevated intraocular pressure (IOP) is a major risk factor for progression of glaucoma, treatment has been based on lowering IOP. We previously demonstrated inducible nitric-oxide synthase (NOS-2) in the optic nerve heads from human glaucomatous eyes and from rat eyes with chronic, moderately elevated IOP. Using this rat model of unilateral glaucoma, we treated a group of animals for 6 months with aminoguanidine, a relatively specific inhibitor of NOS-2, and compared them with an untreated group. At 6 months, untreated animals had pallor and cupping of the optic disks in the eyes with elevated IOP. Eyes of aminoguanidine-treated animals with similar elevations of IOP appeared normal. We quantitated retinal ganglion cell loss by retrograde labeling with Fluoro-Gold. When compared with their contralateral control eyes with normal IOP, eyes with elevated IOP in the untreated group lost 36% of their retinal ganglion cells; the eyes with similarly elevated IOP in the aminoguanidine-treated group lost less than 10% of their retinal ganglion cells. Pharmacological neuroprotection by inhibition of NOS-2 may prove useful for the treatment of patients with glaucoma

Association between low plasma vitamin E concentration and progression of early cortical lens opacities.

Rouhianen PRHSJT.

*Am J Epidemiol.* 1996; 1(144(5)):496-500.

Carotenoids in the retina--a review of their possible role in preventing or limiting damage caused by light and oxygen.

Schalch W.

*EXS.* 1992; 62:280-98.

Two of the circa 600 naturally occurring carotenoids, zeaxanthin and lutein, the major carotenoids of maize and melon respectively, are the constituents of the macula lutea, the yellow spot in the macula, the central part of the retina in primates

and humans. Of the circa ten carotenoids found in the blood these two are specifically concentrated in this area, which is responsible for sharp and detailed vision. This paper reviews the ideas that this concentration of dietary carotenoids in the macula is not accidental, but that their presence may prevent or limit damage due to their physicochemical properties and their capability to quench oxygen free radicals and singlet oxygen, which are generated in the retina as a consequence of the simultaneous presence of light and oxygen. Additionally, *in vitro* and *in vivo* animal experiments are reviewed as well as observational and epidemiological data in humans. These show that there is enough circumstantial evidence for a protective role of carotenoids in the retina to justify further research. Some emphasis will be put on age-related macular degeneration (AMD), a multifactorial degenerative retinal disease for which the exposure to light and thus photochemical damage has been suggested as one of the etiological factors. Recent attempts at nutritional intervention in this condition will also be reviewed

The use of vitamin supplements and the risk of cataract among US male physicians.

Seddon JM, Christen WG, Manson JE, et al.

*Am J Public Health.* 1994 May; 84(5):788-92.

**OBJECTIVES.** The purpose of this study was to examine prospectively the association between reported use of vitamin supplements and risk of cataract and cataract extraction. **METHODS.** The study population consisted of 17,744 participants in the Physicians' Health Study, a randomized trial of aspirin therapy and beta-carotene among US male physicians 40 to 84 years of age in 1982 who did not report cataract at baseline and provided complete information about vitamin supplementation and other risk factors for cataract. Self-reports of cataract and cataract extraction were confirmed by medical record review. **RESULTS.** During 60 months of follow-up, there were 370 incident cataracts and 109 cataract extractions. In comparison with physicians who did not use any supplements, those who took only multivitamins had a relative risk of cataract of 0.73 after adjustment for other risk factors. For cataract extraction, the corresponding relative risk was 0.79. Use of vitamin C and/or E supplements alone was not associated with a reduced risk of cataract, but the size of this subgroup was small. **CONCLUSIONS.** These data suggest that men who took multivitamin supplements tended to experience a decreased risk of cataract and support the need for rigorous testing of this hypothesis in large-scale randomized trials in men and women

Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. Eye Disease Case-Control Study Group.

Seddon JM, Ajani UA, Sperduto RD, et al.

*JAMA.* 1994 Nov 9; 272(18):1413-20.

**OBJECTIVE--**To evaluate the relationships between dietary intake of carotenoids and vitamins A, C, and E and the risk of neovascular age-related macular degeneration (AMD), the leading cause of irreversible blindness among adults. **DESIGN--**The multicenter Eye Disease Case-Control Study. **SETTING--**Five ophthalmology centers in the United States. **PATIENTS--**A total of 356 case subjects who were diagnosed with the advanced stage of AMD within 1 year prior to their enrollment, aged 55 to 80 years, and residing near a participating clinical center. The 520 control subjects were from the same geographic areas as case subjects, had other ocular diseases, and were frequency-matched to cases according to age and sex. **MAIN OUTCOME MEASURES--**The relative risk for AMD was estimated according to dietary indicators of antioxidant status, controlling for smoking and other risk factors, by using multiple logistic-regression analyses. **RESULTS--**A higher dietary intake of carotenoids was associated with a lower risk for AMD. Adjusting for other risk factors for AMD, we found that those in the highest quintile of carotenoid intake had a 43% lower risk for AMD compared with those in the lowest quintile (odds ratio, 0.57; 95% confidence interval, 0.35 to 0.92; P for trend = .02). Among the specific carotenoids, lutein and zeaxanthin, which are primarily obtained from dark green, leafy vegetables, were most strongly associated with a reduced risk for AMD (P for trend = .001). Several food items rich in carotenoids were inversely associated with AMD. In particular, a higher frequency of intake of spinach or collard greens was associated with a substantially lower risk for AMD (P for trend < .001). The intake of preformed vitamin A (retinol) was not appreciably related to AMD. Neither vitamin E nor total vitamin C consumption was associated with a statistically significant reduced risk for AMD, although a possibly lower risk for AMD was suggested among those with higher intake of vitamin C, particularly from foods. **CONCLUSION--**Increasing the consumption of foods rich in certain carotenoids, in particular dark green, leafy vegetables, may decrease the risk of developing advanced or exudative AMD, the most visually disabling form of macular degeneration among older people. These findings support the need for further studies of this relationship

Fruits and vegetables that are sources for lutein and zeaxanthin: the macular pigment in human eyes.

Sommerburg O, Keunen JE, Bird AC, et al.

*Br J Ophthalmol.* 1998 Aug; 82(8):907-10.

**BACKGROUND:** It has been suggested that eating green leafy vegetables, which are rich in lutein and zeaxanthin, may

decrease the risk for age related macular degeneration. The goal of this study was to analyse various fruits and vegetables to establish which ones contain lutein and/or zeaxanthin and can serve as possible dietary supplements for these carotenoids. METHODS: Homogenates of 33 fruits and vegetables, two fruit juices, and egg yolk were used for extraction of the carotenoids with hexane. Measurement of the different carotenoids and their isomers was carried out by high performance liquid chromatography using a single column with an isocratic run, and a diode array detector. RESULTS: Egg yolk and maize (corn) contained the highest mole percentage (% of total) of lutein and zeaxanthin (more than 85% of the total carotenoids). Maize was the vegetable with the highest quantity of lutein (60% of total) and orange pepper was the vegetable with the highest amount of zeaxanthin (37% of total). Substantial amounts of lutein and zeaxanthin (30-50%) were also present in kiwi fruit, grapes, spinach, orange juice, zucchini (or vegetable marrow), and different kinds of squash. The results show that there are fruits and vegetables of various colours with a relatively high content of lutein and zeaxanthin. CONCLUSIONS: Most of the dark green leafy vegetables, previously recommended for a higher intake of lutein and zeaxanthin, have 15-47% of lutein, but a very low content (0-3%) of zeaxanthin. Our study shows that fruits and vegetables of various colours can be consumed to increase dietary intake of lutein and zeaxanthin

Inhibition of cataracts in moderately diabetic rats by aminoguanidine.

Swamy-Mruthinti S, Green K, Abraham EC.

*Exp Eye Res.* 1996 May; 62(5):505-10.

The effect of aminoguanidine (AG), an inhibitor of advanced glycation, on the development of cataracts was studied in diabetic rats. Rats were made diabetic with streptozotocin, and based on the level of plasma glucose they were grouped as moderately (350 mg dl<sup>-1</sup> plasma glucose) diabetic. One half of the animals in each group received AG (25 mg kg<sup>-1</sup> body weight each day), intraperitoneally, starting from the day of streptozotocin injection. Progression of lens opacification was recorded using Fundus and Scheimpflug photography at regular time intervals. On the ninetieth day all the rats were killed and the levels of advanced glycation end products (AGE) was determined by measuring the non-tryptophan fluorescence of the lens soluble and insoluble fractions. Densitometric analysis of Scheimpflug images showed that in diabetic rats lens opacification progressed in a biphasic manner, an initial slow progression for the first 60 days, followed by a steep increase during next 30 days. Moderately and severely diabetic rats developed lens opacities more or less at the same time. AGE fluorescence in the lens soluble fractions increased three-fold and seven-fold in the moderately and severely diabetic rats, respectively; whereas in insoluble fractions there was a 30% and three-fold increase in the moderately and severely diabetic rats, respectively. Although AG treatment inhibited the AGE fluorescence of lens soluble and insoluble fractions by about 56% and 75% in moderately diabetic and by 19% and 52% severely diabetic rats, respectively, the development of cataracts was delayed only in the moderately diabetic rats. These results thus suggest that the effect of AG is indeed inhibition of the formation of AGEs. However, in the severely diabetic rats the beneficial effect of AG is overwhelmed by the excessive accumulation of AGEs

Acetyl- L -carnitine decreases glycation of lens proteins: in vitro studies.

Swamy-Mruthinti S, Carter AL.

*Exp Eye Res.* 1999 Jul; 69(1):109-15.

Although the role of carnitine system in the ocular tissues is not clearly understood, earlier studies showed that lenticular levels of L -carnitine were the highest among ocular tissues and there was a dramatic depletion of lenticular L -carnitine and acetyl- L -carnitine in streptozotocin-diabetic rats. As protein glycation has been implicated in the development of several diabetic complications including cataracts, this study was initiated to show the possible effects of L -carnitine and acetyl- L -carnitine on the glycation and advanced glycation (AGEs) of lens proteins. Calf lens soluble fraction (crystallins) was incubated with 50 m glucose (containing <sup>14</sup>C glucose) with or without 5-50 m ml -carnitine, 5-50 m m acetyl- L -carnitine and 5-50 m m acetyl salicylic acid, for 15 days. The results show that while L -carnitine did not have any effect on in vitro glycation of lens crystallins, acetyl- L -carnitine and acetyl salicylic acid decreased crystallin glycation by 42% and 63%, respectively-this decrease was concentration dependent. Glycated crystallins were separated on HPLC which showed that the rate of glycation is in the following order: alpha>beta>gamma. Interestingly, acetyl- L -carnitine inhibited glycation of alpha crystallin more than other crystallins. In vitro incubations with [<sup>3</sup>H-acetyl] acetyl- L -carnitine showed that acetyl- L -carnitine acetylates lens crystallins (non-enzymatically) and alpha crystallin is the major acetylated protein. Furthermore, there was a 70% reduction in anti-AGE antibody reactivity when 50 m m acetyl- L -carnitine was included in the incubation of lens crystallins and 10 m m erythrose, suggesting that inhibition of glycation by acetyl- L -carnitine also affected the generation of AGEs. This in vitro study shows, for the first time, that acetyl- L -carnitine could acetylate potential glycation sites of lens crystallins, and protect them from glycation-mediated protein damage

Food and nutrient intake and risk of cataract.

Tavani A, Negri E, La Vecchia C.

The relationship between cataract extraction and diet was considered in a case-control study conducted in northern Italy. A total of 207 patients who had cataract extraction and 706 control subjects in a hospital for acute, nonneoplastic, nonoculistic, nondigestive tract diseases were interviewed during their hospital stay. Odds ratios (ORs) and their 95% confidence intervals (CIs), according to the intake of alcohol, coffee, tea, and cola, and frequency of intake of 34 food items and 8 micronutrients were derived from multiple logistic regression equations, including terms for age, sex, education, smoking status, body mass index, diabetes, and total calorie intake. Alcohol, coffee, decaffeinated coffee, tea, and cola intakes were not associated with cataract extraction. Among food items, reduced ORs for cataract extraction (highest tertile of intake compared to the lowest), with a significant inverse trend in risk, were found for intake of meat (OR 0.6, 95% CI 0.4 to 0.9), cheese (OR 0.7, 95% CI 0.5 to 1.0), cruciferae (OR 0.5, 95% CI 0.3 to 0.8), spinach (OR 0.6, 95% CI 0.4 to 0.9), tomatoes (OR 0.5, 95% CI 0.4 to 0.8), peppers (OR 0.7, 95% CI 0.4 to 1.1), citrus fruit (OR 0.5, 95% CI 0.2 to 1.3), and melon (OR 0.5, 95% CI 0.4 to 0.8). A significant increase in risk was found for the highest intake of butter (OR 2.8, 95% CI 1.2 to 6.4), total fat (OR 1.8, 95% CI 1.2 to 2.8), and salt (OR 2.4, 95% CI 1.4 to 4.0) compared to the lowest, and for consumption of oil other than olive oil (OR 1.6, 95% CI 1.1 to 2.2). Among micronutrients, lower ORs for cataract extraction (highest quintile of intake compared to the lowest) were found for intake of calcium (OR 0.5, 95% CI 0.3 to 0.8), folic acid (OR 0.4, 95% CI 0.2 to 0.7), and vitamin E (OR 0.5, 95% CI 0.3 to 1.0), while estimated intakes of methionine, retinol, beta-carotene, and vitamins A, C, and D were not associated. Thus, this study indicates that diet plays a considerable role in the risk of cataract extraction in this Italian population, with a protective action played by some vegetables, fruit, calcium, folic acid, and vitamin E, and an increased risk associated with elevated salt and fat intake

Relations among aging, antioxidant status, and cataract.

Taylor A, Jacques PF, Epstein EM.

*Am J Clin Nutr.* 1995 Dec; 62(6 Suppl):1439S-47S.

Light and oxygen are necessary for the function of the eye. However, when present in excess or in uncontrolled circumstances, they appear to be related, probably causally, to the development of cataract. Compromises of function of the lens and retina with aging are exacerbated by depleted or diminished primary antioxidant reserves, antioxidant enzyme capabilities, and diminished secondary defenses such as proteases. Smoking appears to provide an additional oxidative challenge associated with depletion of antioxidants as well as with enhanced risk for cataract formation. Poor education and lower socioeconomic status are associated with poorer nutrition and are also significantly related to increased risk for these debilities. Optimizing nutrition, including diets rich in fruit and vegetables, may provide the least costly and most practicable means to delay cataract

Use of carnosine as a natural anti-senescence drug for human beings.

Wang AM, Ma C, Xie ZH, et al.

*Biochemistry (Mosc ).* 2000 Jul; 65(7):869-71.

Carnosine is an endogenous free-radical scavenger. The latest research has indicated that apart from the function of protecting cells from oxidation-induced stress damage, carnosine appears to be able to extend the lifespan of cultured cells, rejuvenate senescent cells, inhibit the toxic effects of amyloid peptide (A beta), malondialdehyde, and hypochlorite to cells, inhibit glycosylation of proteins and protein-DNA and protein-protein cross-linking, and maintain cellular homeostasis. Also, carnosine seems to delay the impairment of eyesight with aging, effectively preventing and treating senile cataract and other age-related diseases. Therefore, carnosine may be applied to human being as a drug against aging

Prevention of acetaminophen-induced cataract by a combination of diallyl disulfide and N-acetylcysteine.

Zhao C, Shichi H.

*J Ocul Pharmacol Ther.* 1998 Aug; 14(4):345-55.

Injection of acetaminophen (APAP) (350 mg/kg body weight) into C57BL/6 mice in which cytochrome P450 (CYP) 1A1/1A2 had been induced produced acute cataract and other ocular tissue damage. Treatment of APAP-injected mice with one of the major organosulfides in garlic oil, diallyl disulfide (DADS) (200 mg/kg body weight), prevented cataract development and prolonged survival time. N-acetyl L-cysteine (NAC) (500 mg/kg body weight), a prodrug that stimulates glutathione synthesis, also prolonged survival time but was effective only weakly to prevent cataract formation. A combination of DADS and NAC completely prevented cataractogenesis, and all of the treated animals survived APAP toxicity. Neither DADS nor NAC inhibited CYP 1A1/1A2 induction as determined by their effect on the induction of hepatic microsomal ethoxyresorufin O-dealkylase (ERD)

activity. However, in the in vitro enzyme assay, DADS, but not NAC, was a potent inhibitor of ERD activity ( $IC_{50} = 3.5$  mM). Treatment with DADS or NAC slowed but did not stop the decrease of hepatic glutathione (GSH) content. At 4 hours after APAP injection, hepatic GSH began to increase only when DADS and NAC were administered together. These results suggest that the protective effect of DADS is due to its inhibition of biotransformation of APAP to the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) by CYP 1A1/1A2 enzymes and that NAC provides protection by increasing cellular cysteine level and GSH synthesis, thus facilitating detoxification of NAPQI by glutathione conjugation. Assay of plasma glutamate-pyruvate transaminase activity, an indicator of liver necrosis, showed that treatment with DADS and NAC together effectively protected the liver. Therefore, the decrease of GSH as much as 30% of normal concentration, by itself, is not responsible for liver damage. The primary cause of hepatic necrosis is rapid accumulation of NAPQI

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